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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KANTAMNENI, SHOBHA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,699	DRUZGALA ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-29 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *23-29 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/31/2006 has been entered.

Claims 23-29, and 32-34 are pending, and examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-29, 32, 33, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **enablement requirement, rejection of record**. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The instant claims are drawn to the method for blocking calcium channel in a patient in need of such treatment comprising administering to said patient a specific

type of compounds having the structures shown in claims 23-29, and 34 (**Mibefradil analogs**).

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

The rejected claims are drawn to an invention, which pertains to a **method for blocking a calcium channel in a patient**, by the administration of a calcium channel blocking compound having the structures shown in claims 23-29, and 34.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a method of blocking a calcium channel by administering a compound having structures shown in claims 23-29, and 34. The breadth of the claims includes several compounds of structures shown in claims 23, 24 and 34.

(3). State of the Art / (4) Predictability of the Art:

The relative skill of those in the art is high.

The invention is directed to a method for blocking calcium channel by administering a compound having structures shown in claims 23-29, and 34. Applicants have **not provided any evidence or disclosed tests** for the pharmaceutical use for blocking calcium channel in a patient using the instant compounds. Pharmacological activity in general is highly unpredictable area. It is well established that the enablement varies inversely with the degree of unpredictability of the factors involved, and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839 (1970). The pharmacokinetic profile of a compound is governed by its physiochemical properties. More polar compounds will have low volume of distribution in more lipohilic tissues such as the heart and thus increase the concentration in plasma. For example, the compounds represented with the structure as in claim 23, will have different physiochemical properties. The compound of structure in claim 23, with X = $(CH_2)_6$, and R_1 = C_6 alkyl will have different physical properties such as lipophilicity, binding abilities, hydrolyzability etc. than a compound with X = O, and R_1 = C_1 alkyl substituted with OH or NH2, and thus will have different calcium blocking ability or maybe lack any calcium blocking ability. In the instant case, the claimed invention is highly unpredictable because the claimed compounds represented by structures in claims 23-29, and 34 would not only have different calcium channel blocking ability or lack calcium channel blocking ability, but also different abilities towards enzymatic hydrolysis. Also, the enzymatic hydrolysis of the compounds

represented by structures in claims 23, 24 calcium channel blockers results in metabolites with acidic functional groups. These acidic metabolites will have different distribution in plasma and lipohilic tissues. Thus these novel mibefradil-based compounds and their metabolites of the instant invention have different functional groups and result in different biological properties such as drug-drug interactions, formation of metabolites with different toxicities etc. For example, mibefradil demonstrated efficacy in the treatment of hypertension and angina pectoris in man, but was withdrawn by the manufacturer due to drug-drug interactions based on the inhibition of cytochrome P-450. Thus, the instant claimed invention is highly unpredictable and **Applicant did not provide any factual evidence or testing results to show if these so-called analogs of mibefradil compounds can be used as calcium channel blockers**. Note that one of skill in the art would recognize that instant compounds are Not considered to be analogs of mibefradil compounds, since their structures differ substantially.

(5). Guidance of the Specification / (6). Working Examples:

All of the guidance provided by the specification regarding calcium channel blocking compounds is directed to the following compounds: Verapamil, Diltiazem, Nifedipine, Mibefradil.

In the instant case, **no working examples or tests** are presented in the specification as filed to show if the instant compounds referred to as calcium channel blockers do indeed possess calcium channel blocking ability. Lack of a working example is a critical and crucial factor to be considered, especially in a case involving an

unpredictable and undeveloped art. See MPEP 2164. As discussed above, blocking a calcium channel in a patient in need of such treatment is highly unpredictable.

Moreover, the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court of Mineral Separation v. Hyde, 242 U.S. 262, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of ordinary skill in the art would have to first envision a specific soft calcium channel blocking compound of the instant invention for the treatment, a dosage for each compound, the duration of treatment, route of treatment etc. One would then need to test the compound in the model system to determine whether or not the compound is effective as a calcium channel blocker. One would then also need to test the compound in the model system for side effects and toxicity i.e magnitude of the change in the concentration of active species (parent drug and/ or active metabolite) at the site of pharmacological action and the therapeutic index of the drug. Thus a person of skill in the art would have to engage in **undue experimentation** to test these novel mibefradil-based compounds encompassed in the instant claims and their combination with other drugs to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Response to Arguments

The rejection of claims 23-29, 32, 33, and 34 (in part) under 35 U.S.C. 112, first paragraph is MAINTAINED for reasons as discussed in the Final Office Action dated 08/01/2005, and those found below.

Applicant argues that "As analogs of mibefradil, they are expected to have biological activites similar to those of mibefradil. Therefore, since mibefradil is a known calcium channel inhibitor, it stands to reason that the currently claimed compounds are calcium channel inhibitors." This argument is not persausive because compounds in claim 23, will have different physiochemical properties. The compound of structure in claim 23, with X = (CH2)6, and R1 = C6 alkyl will have different physical propedies such as lipophilicity, binding abilities, hydrolyzability etc. than a compound with X. = O, and R1 = C1 alkyl substituted with OH or NH2, and thus will have different calcium blocking ability or maybe lack any calcium blocking ability. In the instant case, the claimed invention is highly unpredictable because the .claimed compounds represented by structures in claims would not only have different calcium channel blocking abiility or lack calcium channel blocking ability, but also different abilities toward enzymatic hydrolysis.

Applicant remarks that "In fact, the Office, in the office action mailed Febraury 8, 2005, stated that the specification was enabling for calcium channel blocking compounds of structures shown in Figures 1-9 of the specification." These remarks have been considered, and the examiner would like to make it clear that in the office action mailed on Febraury 8, 2005, two 112, first paragraph rejections were made. The rejection that applicant is refering to was made for claims 22, 32, and 33 for the scope of enablement for the compounds as it was not clear what compounds were claimed with respect to the claimed characteristics.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted 05/06/2005 with respect to claim 34 has been fully considered but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for "X= a bond, $(CH2)_n$, S, or $O(CH)_n$, R1 = C2-6 alkyl, R2 = COOR5, R3 = (CH2)-COOR6, R4 as in claim, when -$(CH_2)_{0-1}OR_1$ is $-(CH_2)OR1$ in claim 34. Nowhere can the recitation now added into the

claims be found in the specification. Figure 8, and Figure 9 of the specification disclose compounds, wherein X=O, only when "-$(CH_2)_{0-1}OR_1$ is –$(CH_2)OR_1$".

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that Applicant was in possession of the invention as it is now claimed.

Any claim containing a new limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. See MPEP § 2163- § 2163.07(b) for a discussion of the written description requirement of 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-25, and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Branca et al (US 4,808,605, PTO-892 of record).

Branca et al. teach a method of treating ischemia, arrhythmia, and high blood pressure etc. comprising administering a calcium channel blocking compound of formula I. See abstract, in formula I when R = isopropyl, R1 = F, R_3 = loweralkoxy-lower-alkylcarbonyloxy, R2 = CH_3, X = $(CH_2)_3$, and A = benzimidazolyl the resulting

compound is a homolog of the structure of the instant claim 23 i.e the instant compound has loweralkoxycarbonyloxy instead of loweralkoxy-CH_2carbonyloxy as R3 of Branca. See column 41, EXAMPLE B-EXAMPLE D.

It would have been obvious to one having ordinary skill in the art at the time the invention was made, to employ instant compounds because (1) Branca et al. teaches that the homolog of instant compound (i.e -O-COCH2OR1, instead of –O-COOR1, with all the other groups same) are used as calcium channel blockers 2) a homologous series is a family of chemically related compounds, the composition of which varies from member to member by CH_2 * * *, wherein Chemists knowing the properties of one member would in general know what to expect in adjacent members (*In re Henze*, 85 USPQ 261, 261 (CCPA 1950)). Accordingly, one of ordinary skill in the art would have been motivated to employ the particular compounds as instantly claimed as discussed above because of an expectation of success similar to that taught for its disclosed homolog i.e in a method of blocking calcium channel, absent a showing of unexpected results, homolgous compounds are considered to be obvious.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-25, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kazuhisa et al. (JP 11035483, PTO-892).

Kazuhisa et al. teaches a method of treatment of urinary incontinence comprising administration of T type calcium channel inhibitor, ethanone, 1-[(1S,2S)-2-[2-[[3-(1H-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl]-2-methoxy, compound with registry # RN 220-873-01-8, which differs from instant compound having the structure as in claim 23 (or see figure 10 compound of instant specification), when R2 is F, X= a bond, R1 = CH3, R3 = CH3, R4 = $(CH2)_3$-benzimidazolyl by one (CH2) group, i..e the compound disclosed by Kazuhisa has -X-COCH2OR1, whereas the instant compound has –X-COOR1, when R2 is F, X= a bond, R1 = CH3, R3 = CH3, R4 = $(CH2)_3$-benzimidazolyl. Thus the instant particular compound as discussed above, and the compound in Kazuhisa are homologs.

It would have been obvious to one having ordinary skill in the art at the time the invention was made, to employ instant compounds because (1) Kazuhisa teaches that the homolgue of instant compound (i.e -COCH2OR1, instead of –COOR1, with all the other groups same) are used as calcium channel blockers 2) a homologous series is a family of chemically related compounds, the composition of which varies from member to member by CH_2 * * *, wherein Chemists knowing the properties of one member would in general know what to expect in adjacent members (*In re Henze*, 85 USPQ 261, 261 (CCPA 1950)). Accordingly, one of ordinary skill in the art would have been motivated to employ the particular compounds as instantly claimed as discussed above because of

an expectation of success similar to that taught for its disclosed homolog i.e in a method of blocking calcium channel, absent a showing of unexpected results, homolgous compounds are considered to be obvious.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 7.30am-3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni, Ph.D
Patent Examiner
Art Unit 1617

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER